synergistic interaction over a wide range of doses that affect 5% to 99% of cells (f_a =0.05 to f_a=0.99). In contrast, when the same agent combination is given at a different drug ratio, the interaction is strongly antagonistic over the same f_a range (Ratio 2 in Figure 2, cisplatin: topotecan 1:1).

5   Example 3

Combination effects of doxorubicin and cytosine arabinoside or doxorubicin and mitoxantrone

Doxorubicin: cytosine arabinoside (ratio of 1:0.45) and doxorubicin: methotrexate (ratio of 1:0.36) combinations were tested for additive, synergistic or antagonistic effects using the

10   standard tetrazolium-based colorimetric MTT cytotoxicity assay protocol (Mosmann et al (1983) J Immunol Methods 65(1-2): 55-63) described above. Results from the MTT assay were used to calculate combination effects using the median-effect analysis described in the previous examples. The abovementioned ratios tested were based on ratios used in US patent no. 5736155, Bally et al. As depicted in Figure 3, the above indicated ratios displayed antagonistic

15   combination effects over a substantial range of f_a values. It should be noted that data lying outside f_a ranges of about 0.2 to 0.8 are not reliable.

Example 4

Two agent combinations that exhibit synergistic combination effects

Combinations comprising vinorelbine, cisplatin, sphingosine and edelfosine in combination with

20   sphingosine, edelfosine, camptothecin (topotecan), cisplatin and doxorubicin were tested for additive, synergistic or antagonistic effects using the standard tetrazolium-based colorimetric MTT cytotoxicity assay protocol (Mosmann et al (1983) J Immunol Methods 65(1-2): 55-63). Results from the MTT assay were used to calculate combination effects using the median-effect analysis described in the previous examples. Results are shown in Table III:

TABLE III

Doxorubicin in Combination with Cytosine Arabinoside or Methotrexate

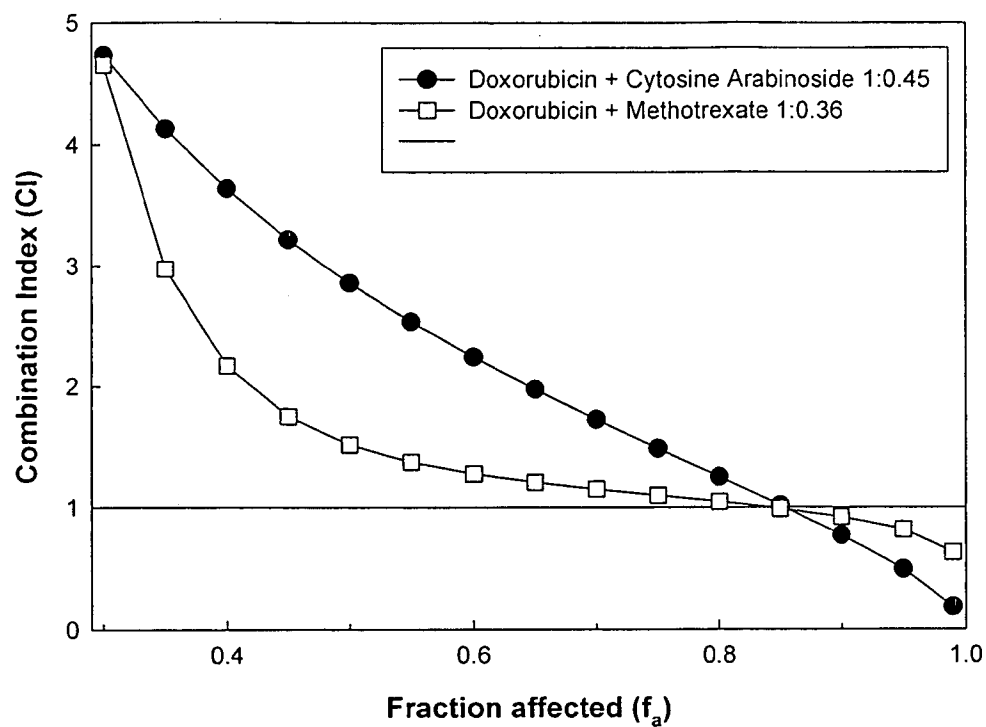**Figure 3**